No new matter is introduced and no change in inventorship results from the amendments made herein.

RESPONSE TO OFFICE ACTION DATED NOVEMBER 19, 2002

Claims 1, 3, 5 - 7, 9, 10 and 18 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, and Bagchi *et al.* Claim 8 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.*, and Burch *et al.* Claims 11 - 17 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.*, and Ansel *et al.* Claims 1, 3, 5 - 7, 9 - 10 and 18 are pending in the instant application.

1. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, and Bagchi *et al.*

Claims 1, 3, 5 - 7, 9, 10 and 18 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, and Bagchi *et al.* Claim 18 is cancelled by the present amendment and therefore the present rejection is moot with respect to that claim. Claims 1, 3, 5 -7, 9 and 10 are still pending. Applicant does not admit that Patel *et al.*, or Guess *et al.*, are prior art under 35 U.S.C. § 102 and reserves the right to overcome this characterization by way of a 37 C.F.R. § 1.131 declaration or otherwise. However, even if, *arguendo*, Patel *et al.*, and/or Guess *et al.*, are available as prior art under 35 U.S.C. 102, Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references when combined must teach or suggest all the claim limitations. See MPEP § 2143.

As will be discussed in detail below, a person of ordinary skill in the art would not have been motivated to modify or combine Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.*, to arrive at Applicant's invention as embodied in Claim 1 as amended herein. Furthermore, even if such motivation had existed, which is not admitted herein, one of ordinary skill in the art would not have combined Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.*, with a reasonable expectation of success. Thirdly, every one of Applicant's claim limitations is not taught by any combination of

Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.* Therefore the asserted *prima facie* case of obviousness fails.

No motivation to combine references so as to arrive at Applicant's invention

Applicant's Claim 1, as amended herein, is directed to a discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients. Further, a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration. Therefore, Applicant's Claim 1 is directed to a composition which is capable of achieving therapeutic effectiveness with a small dose of valdecoxib and within a short period of time after administration to a subject. A person of ordinary skill in the art would not have been motivated to modify or combine Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.* in order to arrive at Applicant's invention.

The Examiner correctly states that Black teaches synthesis of a COX-2 inhibitor and its formulation into a pharmaceutical composition by wet granulation and that Black teaches specific dosages of that COX-2 inhibitor ranging from 10 mg to 250 mg. However, the chemical structure of the Black COX-2 inhibitor is very different from that of valdecoxib. Therefore, the particular dosages described in Black are not necessarily instructive as to dosages appropriate for other COX-2 inhibitors that have different chemical properties. Furthermore, the physical properties (*e.g.* intrinsic solubility) of Black's COX-2 inhibitor are not described. Black indicates that the COX-2 inhibitor disclosed therein is suitable for once- or twice-a-day use; importantly, however, this not due to the drug formulation but rather to the long half-life of the drug itself. See Page 5, lines 22 - 26. Like physical properties, half-life is an attribute inherent in and specific to a particular drug.

The Examiner states that Patel *et al.*, describes a variety of formulations for solid carriers of drugs and various hydrophobic drugs that may be used in the disclosed solid carriers. Patel *et al.* also acknowledges that hydrophobic active ingredients present delivery challenges due to their poor solubility and slow dissolution rate. Column 1, lines 15 - 17. However, Patel *et al.*, when read as a whole, teaches away from Applicant's invention by teaching that at least one ionic or

non-ionic hydrophilic surfactant and/or a lipophilic surfactant or triglyceride is required in order to improve drug dissolution and/or release of such hydrophobic actives. See Column 2, lines 58 - 67, Column 3, lines, 1 - 26, and Column 62, lines 9 - 21.

As such, a person of ordinary skill in the art reading Patel *et al.*, at the time of Applicant's invention would, if anything, believe that at least one ionic or non-ionic hydrophilic surfactant and/or a lipophilic surfactant or triglyceride is needed in order to improve dissolution and/or release of a hydrophobic drug such as valdecoxib. By contrast, Applicant has discovered that valdecoxib compositions capable of providing therapeutically effective blood-drug levels within a surprisingly short time after administration can be prepared with or without such excipients. This is surprising in view of the teaching of Patel *et al.* Optionally, such excipients can be included in Applicant's formulation, if desired, but their presence is not necessary to obtain the advantages of the present invention.

Next, the Examiner states that Bagchi *et al.* teaches the importance of reliable bioavailability, that bioavailability can be improved by decreasing particle size, and that particle sizes of 1 micron to 50 microns may be achieved. Office Action, page 4. Importantly, however, Bagchi *et al.*, describe the extensive problems and limitations of known particle size reduction techniques including, *inter alia*, contamination problems associated with wet milling (Column 1, line 41), low end size limitations of 100 μm and caking problems associated with dry milling (Column 1, line 34), complexities, toxicities and unacceptable amounts of polymer of liposome required for loading of drugs into liposomes (Column 1, lines 45 - 57), and solvent contamination associated with solvent precipitation techniques (column 2, lines 5 - 13).

Bagchi *et al.*, when read as a whole, teaches away from Applicant's invention by teaching that dissolution of drugs of low water solubility can be enhanced by chemical attachment of the drug to photographic coupler molecules to form modified pharmaceutical agents and then dispersing these agents in the presence of a surface modifying and colloid stability enhancing agent (Column 3, lines 21 - 42). If anything, a person of ordinary skill in the art reading Bagchi *et al.*, at the time of Applicant's invention would therefore be motivated to couple valdecoxib to a photographic coupler molecule to form a modified agent and disperse the resulting modified agent in the presence of a surface modifying and colloid enhancing agent in order to improve dissolution. Applicant's invention as embodied in Claim 1 as amended herein does not require

coupling of valdecoxib to a photographic coupler molecule nor does it contemplate a micro-nanoparticulate dispersion in the presence of a surface modifying and colloidal stability enhancing agent. By contrast, Applicant's invention as embodied in amended Claim 1 is directed to discrete solid pharmaceutical compositions. Bagchi *et al.* is not concerned with discrete solid dosage forms and one of ordinary skill in the art would not be motivated to combine Bagchi *et al.* with the other references cited in seeking to develop a discrete solid dosage form having the desired properties.

For at least the above-cited reasons, the teaching of Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.*, would not have provided a person of ordinary skill in the art with the suggestion or motivation to combine said references in order to arrive a Applicant's invention. If anything, such an artisan would have been motivated to attempt to couple valdecoxib to a photographic coupler molecule and form a subsequent dispersion according to the teaching of Bagchi *et al.*, or to prepare a formulation comprising at least one ionic or non-ionic hydrophilic surfactant and/or a lipophilic compound (surfactant or triglyceride) according to the teaching of Patel *et al.* Both of these disclosures expressly teach away from Applicant's invention as embodied in Claim 1 as amended herein.

No reasonable expectation of success

Second, there was, at the time of the present invention, no reasonable expectation of success in formulating a relatively low dose of valdecoxib, an extraordinarily insoluble compound, as a discrete solid dosage form capable of achieving rapid onset of therapeutic effectiveness. Indeed textbook teaching predicted such a dosage form would have low relative bioavailability. Applicant draws to the Examiner's attention the following disclosure in Remington: The Science and Practice of Pharmacy, 19th edition, Volume 1, Chapter 43: Clinical Pharmacokinetics, by Rollins (1995), at page 742 (copy enclosed herewith for the Examiner's convenience), second column, second full paragraph:

> A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases.

After the amendment proposed herein, Applicant's Claim 1 is directed to discrete solid

pharmaceutical compositions. Examiner relies on Bagchi *et al.*, for the proposition that bioavailability can be improved by decreasing particle size, thereby increasing the total drug particle surface area. Office Action, page 4. However, as indicated by the above-quoted passage, it was well known in the art at the time of Applicant's invention that when a drug is formulated as a discrete solid composition (*e.g.* packed into hard gelatin capsules or compressed as a tablet), its bioavailability decreases. Therefore, one of skill in the art at the time of Applicant's invention would not have been motivated to try formulating valdecoxib as a discrete solid dosage form with the expectation of achieving good bioavailability and/or rapid onset.

Surprisingly and in contrast to the teachings of Bagchi *et al.* and Patel *et al.*, in view of the textbook teaching at the time of Applicant's invention, Applicant has discovered excellent onset time and bioavailability with a relatively low dose of valdecoxib formulated as a discrete solid pharmaceutical composition.

Guess *et al.*, does not remedy the defects of Black, Patel *et al.*, and Bagchi *et al.* Guess *et al.*, teaches that a tachykinin receptor antagonist may be administered in combination with valdecoxib. No specific amounts of valdecoxib are disclosed therein and onset time is not discussed.

For at least the above-cited reasons, the teaching of Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.*, even if motivation to combine had existed, which is not admitted herein, would not have provided a person of ordinary skill in the art with a reasonable expectation of success in arriving at Applicant's invention.

Each and every element of Applicant's Claims not disclosed in any combination of references

Applicant's Claim 1 as amended herein is directed to a discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients; a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration.

None of Black, Patel *et al.*, Guess *et al.*, or Bagchi *et al.*, individually discloses a discrete solid pharmaceutical composition comprising about 5 mg to about 40 mg of particulate valdecoxib. Furthermore, none of Black, Patel *et al.*, Guess *et al.*, or Bagchi *et al.*, individually

discloses a discrete solid valdecoxib composition wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time to reach a valdecoxib blood serum concentration of 20 ng/ml of not greater than about 0.5 hours after administration.

Therefore, the combination of Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.* does not teach or suggest all the limitations of Claim 1 as amended herein and thereby lacks the third element necessary for establishing a *prima facie* case of obviousness (MPEP §2143). Because Claims 3, 5-7, 9, and 10 depend from and further limit Claim 1, the combination of Black, Patel *et al.*, Guess *et al.*, and Bagchi *et al.* also does not teach or suggest all the limitations of these claims.

Conclusion: no prima facie case for obviousness can be made against claims 3, 5-7, 9, and 10

Because all three elements of the test for *prima facie* obviousness as set out in MPEP § 2143 have not been met, no *prima facie* case for obviousness can be made. Withdrawal of the rejection under 35 U.S.C. §103(a) as unpatentable over Black in view of Patel *et al.*, Guess *et al.*, and Bagchi *et al.*, is therefore respectfully requested.

2. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.* and Burch *et al.*

Claim 8 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.* and Burch *et al.* Applicant does not admit that Patel *et al.*, or Guess *et al.*, are prior art under 35 U.S.C. § 102 and reserves the right to overcome this characterization by way of a 37 C.F.R. § 1.131 declaration or otherwise. However, even if, *arguendo*, Patel *et al.*, and/or Guess *et al.*, are prior art under 35 U.S.C. 102, Applicant respectfully traverses this rejection.

As stated above, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references when combined must teach or suggest all the claim limitations. See MPEP § 2143. As will be discussed below, each and every element recited in Applicant's Claim 8 is not disclosed in any combination of Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et*

al. and Burch *et al.*

Each and every element of Applicant's Claims not disclosed in any combination of the references

Claim 8 is directed to a discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients. A single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration. Additionally, the composition further comprises one or more opioid or analgesic drugs.

None of Black, Patel *et al.*, Guess *et al.*, Bagchi *et al.*, or Burch *et al.*, individually discloses a discrete solid pharmaceutical composition comprising about 5 mg to about 40 mg of particulate valdecoxib. Furthermore, none of Black, Patel *et al.*, Guess *et al.*, Bagchi *et al.*, or Burch *et al.*, individually discloses a discrete solid valdecoxib composition wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time to reach a valdecoxib blood serum concentration of 20 ng/ml of not greater than about 0.5 hours after administration.

Conclusion: no prima facie case for obviousness can be made against Claim 8

Therefore, the combination of Black, Patel *et al.*, Guess *et al.*, Bagchi *et al.* and Burch *et al.*, does not teach or suggest all the limitations of Claim 8 and thereby lacks the third element necessary for establishing a *prima facie* case of obviousness (MPEP §2143). Withdrawal of the rejection under 35 U.S.C. § 103(a), as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.* and Burch *et al.*, is therefore respectfully requested.

3. Rejection under 35 U.S.C. § 103(a), as being unpatentable over Black in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.* and Ansel *et al.*

Claims 11 - 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable in view of Patel *et al.*, Guess *et al.*, Bagchi *et al.*, and Ansel *et al.* As indicated hereinabove, Claims 11 - 17 are cancelled by the present amendment in order to expedite prosecution of a presently preferred embodiment of the invention. As such, this rejection is now moot. Applicant reserves the right to

reintroduce the subject matter of one or more presently cancelled claims in continuing application(s).

Conclusion

Claims 1, 3, 5 - 7, 9, 10 and 18, following amendment as proposed herein, are believed to be in condition for allowance. No fee is believed payable in connection with the present amendment and Response to Office Action; however, if it is determined that a fee is payable, please charge Deposit Account No. 19-1025, in the name of Pharmacia Corporation.

Respectfully submitted,

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Attachments:
Marked up version of amendments made
Rollins (1995) reference cited in Response.

MARKED UP VERSION OF AMENDMENTS MADE

IN THE CLAIMS

1. (Twice Amended) A discrete solid pharmaceutical composition comprising particulate valdecoxib in an amount of about 5 mg to about 40 mg per dose and one or more pharmaceutically acceptable excipients, wherein a single oral administration of the composition, in an amount containing about 20 mg of valdecoxib, to a fasting subject provides a time course of blood serum concentration of valdecoxib having a time to reach a concentration of 20 ng/ml not greater than about 0.5 h after administration.

IN THE SPECIFICATION

Page 3

Lines 27 - 28:

[Figure 3 is a graph showing plasma concentration of valdecoxib in dogs following oral administration of valdecoxib tablets of the invention.]

Lines 29 – 30:

Figure [4]3 is a graph showing plasma concentration of valdecoxib in humans following oral administration of valdecoxib tablets of the invention.

Page 24

Lines 7 – 14:

Example 4 is deleted.

Line 15:

Example [5]4: Pharmacokinetic properties of valdecoxib in humans

Drawing Sheet 3 of 3

Figure 3 is deleted.

The legend for former Figure 4 has been changed as follows: -- Fig. [4]3 --

Remington: The Science and Practice of Pharmacy . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

AUTHORS

The 112 chapters of this edition of *Remington* were written by the editors, by members of the Editorial Board, and by other authors listed on pages x to xii.

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When treating a patient in which a rapid (but not immediate) effect is required (as with asymptomatic ventricular premature contractions), it is advisable to use a dosage form to initiate therapy that is absorbed rapidly and completely. Once the drug is shown to be effective in a particular patient, the dosage form can be changed to one with characteristics similar to *B*, so that less-frequent dosing is required and patient compliance is improved.

The preparation represented by *C in the same dose* as *A* or *B* is probably not an acceptable way to administer this drug. The total amount of drug *C* that is absorbed is only half of that of *B* (area-under-the-plasma concentrations-time curve, AUC, for *C* is half of the AUC for *B*). Thus, it would require twice the dose to attain blood levels equivalent to *A* or *B*.

The treatment of asthma with theophylline is an example in which a rapidly absorbed dosage form is used to initiate therapy and a prolonged-release dosage form is used for maintenance therapy. When a patient has an acute asthma attack or worsening bronchitis that requires bronchodilator therapy, it is advisable to use the theophylline-ethylenediamine complex (aminophylline). This dosage form can be administered either intravenously or orally; the former should be used to initiate treatment in the acute asthmatic patient who requires prompt therapy, so that neither a delay in achieving therapeutic plasma concentrations nor bioavailability are factors in the initial therapeutic response.

Following the administration of an aminophylline loading dose (see under *Distribution*, page 743), the drug should be given by continuous intravenous infusion until the acute symptoms have subsided, which may take 24 to 72 hours. In the patient with less-severe symptoms, aminophylline can be administered orally four times a day. Once the patient's condition has improved and an effective dose of theophylline has been established, then it may be possible to switch the patient to a prolonged-release formulation for maintenance therapy.

The absorption and bioavailability of Theodur and Sustaire, two sustained-release theophylline preparations, permit 12-hour dosing intervals; Slo-Phyllin Gyrocaps should be given every 8 hours. The total daily dose of theophylline that was required during intravenous aminophylline administration is divided into smaller oral doses given at intervals appropriate for the characteristic of the preparation or dosage form used.

It is important to keep in mind that the absorption and plasma-time curve characteristics for these preparations usually have been established in healthy volunteers or asthmatic patients without other illnesses. Patients who eliminate theophylline rapidly (ie, smokers) may have increased dosage requirements, and the dosage interval may have to be shortened to avoid recurrent asthmatic symptoms between doses.

Prolonged-release dosage forms have the additional advantage that fluctuations in blood levels of the drug will be less than with rapidly absorbed dosage forms. There is evidence for some drugs that the reduction in rapidly changing blood levels may improve efficacy and decrease adverse effects. For example, the dose of fentanyl or ketamine required to maintain anesthesia was reduced by nearly 50% when the drugs were given by continuous infusion rather than by intermittent bolus.[2]

This reduced dose also resulted in more rapid recovery with less-prolonged sedation. These findings suggest that a reduction of fluctuation in the plasma concentrations will reduce total dosage requirement. If such a reduction in plasma concentration fluctuation also applies to oral prolonged-release dosage forms, it would provide a distinct advantage for their use.

The bioavailability of a particular drug product, by any route of administration, can be determined by comparison of the AUC of a drug given by the route of interest with that of the same dose given intravenously (see Chapter 41). In the case of an orally administered drug, it is the ratio of the AUC after an oral dose to the AUC after an intravenous dose. The decreased bioavailability of an oral dose may be due to poor gastrointestinal absorption of the drug because it does not go completely into solution, as it may be degraded in the gastrointestinal lumen, or it does not pass across the intestinal mucosa. Furthermore, in order to reach the general circulation, drugs taken orally must pass through the wall of the gastrointestinal tract and then to the liver via the portal vein. Thus, drug metabolism may occur in the gut wall or in the liver and severely limit the delivery of parent drug to the general circulation.

If the extraction of the drug by the liver is efficient, oral administration results in low bioavailability and sometimes limited pharmacological effect. This is commonly referred to as *first-pass metabolism* (presystemic metabolism). Table 1 lists some of the drugs known to exhibit first-pass metabolism. Because their extraction is high and their rate of metabolism great, the rate- limiting step in the clearance of drugs in Table 1 is liver blood flow. The metabolism of these drugs can be referred to as *flow-limited*. The clinical significance of changes in liver blood flow on drug bioavailability will be discussed under *Drug Therapy in Hepatic Disease*.

Different dosage forms of the same drug may have different systemic bioavailabilities. The ratio of the AUC for one dosage form to that of another dosage form is termed the *relative bioavailability*. A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases. Furthermore, a drug in one dosage form made by one manufacturer may have a different bioavailability from that of another manufacturer.

With drugs for which bioavailability varies significantly from product to product, if one product initially has been efficacious, it is advisable to continue with that product. If for economical or other reasons the product must be changed to that manufactured by a different company, it is wise to observe the patient carefully for a possible change in clinical response indicative of a change in bioavailability. Products designed for prolonged release sometimes have a low bioavailability. However, this may not be a problem during maintenance therapy so long as therapeutic serum concentrations are achieved consistently.

The presence of food in the stomach or intestine can have a profound influence on the rate and extent (bioavailability) of drug absorption. Initial absorption studies for a new drug, performed in healthy volunteers, commonly include fasting and nonfasting conditions. Therefore, in general, and for controlled diets, the effect that food may have on drug absorption may be known when a drug is introduced into the market. Unfortunately, food-drug interactions are not consistent, and the presence of food may enhance or diminish the absorption of drugs. The most common type of interaction occurs when a food constituent binds the drug and the food-drug complex cannot pass through the gut wall. For example, complexation of tetracycline antibiotics may occur when these drugs are administered with dairy products or with antacids containing aluminum, calcium or magnesium.

The presence of a large meal in the stomach will delay gastric emptying. If a drug that is absorbed in the intestine is ingested with a large meal, the delay in gastric emptying may result in a delay in absorption of the drug. However, the presence of food in the stomach also has been shown to

Table 1—Drugs that Exhibit First-Pass Metabolism

Acetylsalicylic acid	Morphine
Alprenolol	Nitroglycerin
Amitriptyline	Nortriptyline
Desipramine	Pentazocine
Dopamine	Prazosin
Imipramine	Propoxyphene
Isoproterenol	Propranolol
Lidocaine	Salicylamide
Meperidine	Verapamil
Metoprolol	